Complete Summary

GUIDELINE TITLE

Management of Crohn's disease in adults.

BIBLIOGRAPHIC SOURCE(S)

Hanauer SB, Sandborn W. Management of Crohn's disease in adults. Am J Gastroenterol 2001 Mar;96(3):635-43. [128 references]

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Crohn's disease

GUIDELINE CATEGORY

Diagnosis
Management

CLINICAL SPECIALTY

Family Practice
Gastroenterology
Internal Medicine
Surgery

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To suggest preferable approaches to the diagnosis and management of Crohn's disease

TARGET POPULATION

Patients with Crohn's disease

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis

1. General examination
    - Evaluation of signs and symptoms
    - Physical examination
    - Laboratory tests, including tests for fecal leukocytes and presence of enteric pathogens, ova, or parasites, and Clostridium difficile
2. Radiological examination, including contrast radiography, radio-labeled leukocyte scan, abdominal or endoscopic ultrasonography, computed tomography, or magnetic resonance imaging
3. Upper and lower endoscopy, including endoscopic biopsy
4. Assessment of exacerbating factors, such as intercurrent infection, cigarette smoking, and use of nonsteroidal anti-inflammatory drugs
5. Determination of disease activity

Management

Mild-moderate active disease

1. Oral aminosalicylates, such as mesalamine or sulfasalazine
2. Metronidazole
3. Ciprofloxacin
4. Controlled ileal release budesonide

Moderate-severe disease

1. Prednisone
2. Budesonide (not approved by the U.S. Food and Drug Administration)
3. Antibiotic therapy or drainage (percutaneous or surgical) for infection
4. Infliximab

Note: Azathioprine, mercaptopurine, methotrexate, and addition of an aminosalicylate to corticosteroids are also considered, but not recommended. Elemental diet, liquid polymer diets, and elimination diets are also considered but not recommended.

Severe-fulminant disease

1. Hospitalization
2. Percutaneous or surgical drainage of abscesses
3. Parenteral corticosteroids or adrenocorticotrophic hormone (ACTH)
4. Nutritional support via elemental feeding or parenteral hyperalimentation

Note: Cyclosporine and tacrolimus* are considered but not specifically recommended for severe-fulminant disease.

Perianal disease (acute phase)

1. Surgical drainage with or without placement of setons
2. Antibiotics, such as metronidazole alone or in combination with ciprofloxacin
3. Immunosuppressives, such as cyclosporine, tacrolimus*, azathioprine, or mercaptopurine
4. Infliximab

*Note from the National Guideline Clearinghouse: On March 10, 2005, the U.S. Food and Drug Administration (FDA) issued a Public Health Advisory to inform healthcare providers and patients about a potential cancer risk from use of Elidel (pimecrolimus) and Protopic (tacrolimus), products that are applied to the skin. This concern is based on information from animal studies, case reports in a small number of patients, and how these drugs work. It may take human studies of ten years or longer to determine if use of Elidel or Protopic is linked to cancer. In the meantime, this risk is uncertain and FDA advises that Elidel and Protopic should be used only as labeled, for patients who have failed treatment with other therapies. See the FDA Web site for more information.

Maintenance therapy

1. Corticosteroids (considered but not recommended)
2. Azathioprine/mercaptopurine after inductive therapy with corticosteroids
3. Mesalamine or azathioprine/mercaptopurine after ileocolonic resections

Surgical treatment for medically refractory disease

1. Surgical resection, including colectomy and ileostomy
2. Strictoplasty
3. Drainage of abscesses

MAJOR OUTCOMES CONSIDERED

- Relief of symptoms
- Clinical remission rates
- Closure of Crohn's disease fistulae
- Endoscopic and clinical recurrence rates
- Incidence of adverse effects

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The guideline developers performed electronic literature searches using Medline and other literature search tools. Expert authors reviewed these results, and supplemented them, as appropriate, with very recent materials.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Not stated

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review
Review of Published Meta-Analyses

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not applicable

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

These guidelines are developed under the auspices of the American College of Gastroenterology and its Practice Parameters Committee. Expert opinion is solicited from the outset for the document. The Committee reviews guidelines in depth, with participation from experienced clinicians and others in related fields.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Diagnosis

The diagnosis of Crohn's disease is based upon a composite of endoscopic, radiographic, and pathological findings documenting focal, asymmetric, transmural, or granulomatous features. The sequence of diagnostic maneuvers is based upon presenting symptoms, physical findings, and basic laboratory abnormalities.

General

Crohn's disease should be considered for patients presenting with chronic or nocturnal diarrhea, abdominal pain, bowel obstruction, weight loss, fever, night sweats, or symptoms reflecting underlying intestinal inflammation, fibrosis, or fistula. Alternative inflammatory bowel diseases (infectious, ischemic, radiation-induced, medication-induced, particularly nonsteroidal anti-inflammatory drugs), or idiopathic (ulcerative colitis, celiac disease, or microscopic colitis), and irritable bowel syndrome comprise the major differential diagnoses. The presence of fecal leukocytes confirms intestinal inflammation. In the presence of diarrhea at presentation or relapse, stools should be examined for enteric pathogens, ova and parasites, and Clostridium difficile. Serological studies such as antibodies against Saccharomyces cerevisiae are evolving to support the diagnosis of Crohn's disease but may not be sufficiently sensitive or specific to be practical as screening tools.

Radiological features

Diagnosis of Crohn's disease can be accomplished by contrast radiography (air contrast barium enema, small bowel follow through, or enteroclysis) to confirm disease location and intestinal complications. Radio-labeled leukocyte scans can discriminate between inflammatory and noninflammatory features and may be used occasionally in clinical practice when there is a discrepancy between clinical symptoms and structural or anatomic studies. Abdominal or endoscopic ultrasonography, computerized tomography, or magnetic resonance imaging can delineate and discriminate intra-abdominal masses/abscesses or perianal complications.

Endoscopy

Upper or lower gastrointestinal (GI) endoscopy is used to confirm the diagnosis of Crohn's disease, assess disease location, or obtain tissue for pathological evaluation. Colonoscopic evaluation of surgical anastomoses can be used to predict the likelihood of clinical relapse and assess response to postoperative therapy. Endoscopic biopsy can establish the diagnosis, differentiate between ulcerative colitis and Crohn's disease, rule out acute self-limited colitis, or identify dysplasia or cancer.

Exacerbating factors

Factors recognized to exacerbate Crohn's disease include: intercurrent infections (both upper respiratory tract and enteric infections, including Clostridium difficile), cigarette smoking, and nonsteroidal anti-inflammatory drugs. The issue of stress initiating or exacerbating Crohn's disease remains controversial.

Determining disease activity

Therapeutic options are determined by an assessment of the disease location, severity, and extraintestinal complications. In the absence of a "gold standard" measure of disease activity, severity is established on clinical parameters, systemic manifestations, and the global impact of the disease on the individual's quality of life. Additional factors that impact on therapy include the assessment of growth and nutrition, extraintestinal complications, therapy-induced complications, functional ability, social and emotional support and resources, and education about the disease.

Working definitions of Crohn's disease activity are described below:

- MILD-MODERATE DISEASE. Mild-moderate Crohn's disease applies to ambulatory patients able to tolerate oral alimentation without manifestations of dehydration, toxicity (high fevers, rigors, prostration), abdominal tenderness, painful mass, obstruction, or >10% weight loss.
- MODERATE-SEVERE DISEASE. Moderate-severe disease applies to patients who have failed to respond to treatment for mild-moderate disease or those with more prominent symptoms of fevers, significant weight loss, abdominal pain or tenderness, intermittent nausea or vomiting (without obstructive findings), or significant anemia.
- SEVERE-FULMINANT DISEASE. Severe-fulminant disease refers to patients with persisting symptoms despite the introduction of steroids as outpatients, or individuals presenting with high fever, persistent vomiting, evidence of intestinal obstruction, rebound tenderness, cachexia, or evidence of an abscess.
- REMISSION. Remission refers to patients who are asymptomatic or without inflammatory sequelae and includes patients who have responded to acute medical intervention or have undergone surgical resection without gross evidence of residual disease. Patients requiring steroids to maintain well-being are considered to be "steroid-dependent" and are usually not considered to be "in remission."

Management

General

Therapeutic recommendations depend upon the disease location, severity, and complications. Therapeutic approaches are individualized according to the symptomatic response and tolerance to medical intervention. Therapy is sequential to treat "acute disease" then to "maintain remission." Surgery is advocated for obstructing stenoses, suppurative complications, or medically intractable disease. Narcotic analgesia should be avoided except for the perioperative setting because of the potential for tolerance and abuse in the setting of chronic disease.

Mild-Moderate Active Disease

Ileal, ileocolonic, or colonic disease is treated with an oral aminosalicylate (mesalamine 3.2-4 g or sulfasalazine 3-6 g daily in divided doses). Alternatively, metronidazole 10-20 mg/kg/day may be effective in a proportion of patients not responding to sulfasalazine. Ciprofloxacin 1 g daily is equally effective to mesalamine, and controlled ileal release budesonide may become an available alternative in the near future.

Response to initial therapy should be evaluated within several weeks. Treatment for active disease should be continued to the point of symptomatic remission or failure to continue improvement. Patients achieving remission should be considered for maintenance therapy. Those with continued symptoms should be treated with an alternative therapy for mild-moderate disease or advanced to treatment for moderate-severe disease according to their clinical status.

Moderate-Severe Disease

Patients with moderate-severe disease are treated with prednisone 40-60 mg daily or budesonide 9 mg daily (currently not Food and Drug Administration approved), until resolution of symptoms and resumption of weight gain (generally 7-28 days). Infection or abscess requires appropriate antibiotic therapy or drainage (percutaneous or surgical). Infusions of infliximab are an effective adjunct and may be an alternative to steroid therapy in selected patients in whom corticosteroids are contraindicated or ineffective.

Severe-Fulminant Disease

Patients with persisting symptoms despite introduction of oral steroids or infliximab, or those presenting with high fever, frequent vomiting, evidence of intestinal obstruction, rebound tenderness, cachexia, or evidence of an abscess should be hospitalized. Surgical consultation is warranted for patients with obstruction or tender abdominal mass. An abdominal mass should be evaluated via ultrasound or computerized tomography to exclude an abscess. Abscesses require percutaneous or surgical drainage. Once an abscess has been excluded or if the patient has been receiving oral steroids, parenteral corticosteroids equivalent to 40-60 mg of prednisone are administered in divided doses or as a continuous infusion. There is no specific role for total parenteral nutrition in addition to steroids. Nutritional support via elemental feeding or parenteral hyperalimentation is indicated, after 5-7 days, for patients unable to maintain nutritional requirements.

Perianal Disease

Acute suppuration is an indication for surgical drainage with or without placement of setons. Noncomparative, chronic fertilization, or perianal fissuring is treated medically with antibiotics, immunosuppressives, or infliximab.

Maintenance Therapy

Corticosteroids should not be used as long-term agents to prevent relapse of Crohn's disease. Azathioprine/mercaptopurine have demonstrable maintenance benefits after inductive therapy with corticosteroids. Mesalamine or azathioprine/mercaptopurine should be considered after ileocolonic resections to reduce the likelihood of symptomatic recurrence.

Indications for Surgery

Surgical resection, stricturoplasty, or drainage of abscesses are indicated to treat complications or medically refractory disease.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is not specifically stated for each recommendation.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

General

- Accurate diagnosis and effective management of Crohn's disease may result in relief of symptoms and improved quality of life.

Mild-moderate disease

- In large controlled clinical trials completed in the 1970's and 1980´s one half of the patients receiving sulfasalazine demonstrated a "clinical remission."
- Metronidazole was compared to placebo for mild-moderate disease and was more effective for ileocolitis and colitis than for isolated ileal disease.
- Ciprofloxacin 1 gram daily has been evaluated in a short, 6-week controlled trial and compared to mesalamine 4 grams daily. Approximately 50% of patients in each group achieved a clinical remission.

Moderate-severe disease

- Clinical remission has been reported in 50-70% of patients receiving prednisone.
- Enteric coated formulations of budesonide, 9 mg daily, have been evaluated for treatment of active ileal and ileocecal Crohn's disease with consistent benefits comparable to prednisone or prednisolone, 40 mg daily and superior to placebo.
- Therapy with infliximab is effective for treatment of Crohn's disease patients who have not responded to aminosalicylates, antibiotics, corticosteroids, or immunomodulators. Improvement at 4 weeks was observed in over 80% of patients treated with 5 mg/kg, and over 50% achieved a clinical remission.

Perianal disease

- A placebo-controlled trial has demonstrated benefits from a series of infliximab, in the closure of Crohn's disease fistulae that had not responded to prior therapy with antibiotics, corticosteroids, or immunomodulatory agents. A total of 68% and 55% of patients achieved closure of at least one, or all fistulae for at least 4 weeks.

Maintenance therapy

- Azathioprine and mercaptopurine have been effective in allowing reduction in steroid doses and maintaining remissions after steroid-inductive therapy.
- Treatment with sulfasalazine at doses >3 grams daily and mesalamine, $\geq$3 grams daily reduced the risk of postoperative recurrence for up to 3 years in subgroups of patients. Short-term administration of high-dose metronidazole, 20 mg/kg, also can reduce the likelihood of recurrence for up to 1 year.

POTENTIAL HARMS

- Steroids. Steroid-related side effects are encountered less often with short-term budesonide compared to prednisolone, but some degree of adrenal suppression can be anticipated.
- Infliximab. Infliximab infusions have been associated with both acute and delayed infusion reactions including delayed hypersensitivity (serum sickness-like) reactions, particularly after prolonged intervals (>12 weeks) subsequent to an initial treatment. Other adverse events include the development of antichimeric (HACA) and anti-DNA antibodies.
- Intravenous adrenocorticotrophic hormone (ACTH). Potentially complicated by adrenal hemorrhage
- Antibiotics. The safety of long-term antibiotic therapy has not been established, and patients treated with metronidazole should be monitored for evidence of peripheral neuropathy.
- Azathioprine/Mercaptopurine. Complete blood counts must be monitored carefully early in the course of maintenance treatment and long term, at a minimum of every 3 months because of the risk of delayed neutropenia. Pancreatitis, typically presenting several weeks after initiating therapy, occurs in approximately 3-15% of patients and recurs with re-introduction of either azathioprine or mercaptopurine. An increase risk of neoplasia has not been observed with the use of purine analogues for inflammatory bowel disease.

Subgroups Most Likely to be Harmed:

- Over 50% of patients treated acutely with corticosteroids will become "steroid dependent" or "steroid resistant," particularly smokers, or those with colonic disease
- Younger patients, those with colonic disease, and cigarette smokers are more likely to become steroid dependent

QUALIFYING STATEMENTS

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Guidelines are intended to be flexible, not necessarily indicating the only acceptable approach, and should be distinguished from standards of care that are inflexible and rarely violated. Given the wide range of choices in any health care problem, the physician should select the course best suited to the individual patient and the clinical situation presented.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Hanauer SB, Sandborn W. Management of Crohn's disease in adults. Am J Gastroenterol 2001 Mar;96(3):635-43. [128 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2001 Mar

GUIDELINE DEVELOPER(S)

American College of Gastroenterology - Medical Specialty Society

SOURCE(S) OF FUNDING

American College of Gastroenterology

GUIDELINE COMMITTEE

Ad Hoc Practice Parameters Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Authors: Stephen B. Hanauer, MD; William Sandborn, MD

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available from the American Journal of Gastroenterology Online.

Print copies: Available from the American College of Gastroenterology, 4900 B South 31st St, Arlington, VA 22206-1656; Web site: www.acg.gi.org.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on September 7, 2001. The information was verified by the guideline developer on November 7, 2001. This summary was updated by ECRI on March 15, 2005 following release of a public health advisory from the U.S. Food and Drug Administration regarding the use of Elidel.

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